NEUROLOGICAL SEQUELAE OF SPINAL ANESTHESIA

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SPINAL anesthesia, first performed by Corning in 1885 and introduced clinically by Bier in 1899, has been the subject of controversy ever since. This controversy, often more emotional than objective, has centered around permanent neurological deficits associated with the technique. The first of these was reported in 1906 [46] and since that time innumerable reports of single cases or series of cases of neurological impairment have appeared. This has led some to condemn the technique, a position vehemently attacked by others who believe the technique to be without complications. A few take the middle road and attempt to show that both extremes have some validity and that the truth lies in between. Enough work has been done on spinal anesthesia so that it is now possible to evaluate the question of neurologic damage with objectivity. It is the purpose of this article to do this.

CLASSIFICATION

Neurological complications associated with spinal anesthesia may be divided into two categories, those which coincide with but are unrelated to the anesthesia, and those which are causally and directly related to the anesthesia. The former group is important because its inclusion in discussions of neurological complications due to spinal anesthesia leads to confusion regarding the incidence, pathogenesis, and treatment of those neurological disorders which are truly due to the anesthesia itself. Such disorders include pre-existing neurological diseases which progress naturally, their course being essentially unaltered by the administration of spinal anesthesia (*e.g.*, carcinomas metastatic to the spine).[50] Also included are pre-existing neurological diseases which would be expected to cause severe neurological symptoms in the near future but manifestation of the symptoms appears to have been accelerated by the spinal anesthetic. The frequent appearance of the signs of spinal cord meningiomas in association with spinal anesthesia [25, 62, 64] is an example of this group. In this category are also neurological disorders which appear immediately following spinal anesthesia but which are due to intraoperative or postoperative factors. These are often iatrogenic and include not only surgical damage to nerves but also peripheral neuropathies due to pressure from improper positioning of the patient on the operating table or from improperly applied plaster casts, etc.[55] Finally, there are idiopathic neurological disorders mimicking the deficits seen after spinal anesthesia but which develop following other types of anesthesia or no anesthesia at all.[1, 9, 14, 19, 22, 74, 76, 89] Failure to recognize the fortuitous nature of these conditions by consultants who are either biased or unacquainted with modern anesthetic techniques has led to unnecessary confusion (and litigation). These conditions will not be dealt with in detail in the present review, but their occurrence should be borne in mind. They constitute a major source of the neurological complications seen in association with spinal anesthesia as demonstrated by Marinacci [60, 61] who examined 542 patients with neurological deficits suspected of being due to spinal anesthesia. In only 4 cases were the lesions found to be related to the anesthesia, and in 2 of these the relationship was doubtful. In the remaining 538 cases, the neurological disorders bore an apparent but no real relationship to the anesthesia. Marinacci describes, for example, 11 patients with cauda equina syndromes identical to those seen after spinal anesthesia, but none of whom had received spinal anesthesia.[60]

Neurological complications which properly can be ascribed to spinal anesthesia are intradural in origin. Spinal anesthesia has no direct effect on extradural nerve tissue. The intradural complications may be divided into those which involve primarily the spinal cord,

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its enveloping membranes, and its nerve roots, and those which involve primarily the cranial portions of the central nervous system. The intracranial complications include discrete neuropathies involving cranial nerves, a topic to be considered separately, as well as a variety of disorders consequent to vascular accidents the result of alterations in cerebral blood flow during the period of anesthesia. Such changes may be associated with arterial hypertension, but are usually the result of hypotension and decreases in cardiac output with consequent decreases in cerebral blood flow.[16] Inasmuch as cerebral damage due to inadequate cardiac output or cardiac arrest is not peculiar to spinal anesthesia, and inasmuch as there is no evidence to indicate it occurs more frequently with spinal anesthesia than with other forms of anesthesia, this neurological disorder will not be considered in the present review. Attention will instead be centered on those neurological complications which involve neural elements in the spinal subarachnoid space and which can properly be ascribed to the anesthesia. Postspinal headaches will not be considered, but postspinal meningitis will be because of its possible relationship to the development of neurological sequelae.

Incidence

The frequency with which neurological complications occur due to spinal anesthesia is difficult to determine. A review of the literature indicates that even with elimination of the aforementioned coincidental neurological disorders the apparent incidence is high in some series and negligible in others. Part of this discrepancy is related to the methods used in determining incidence. One method, perhaps the least valuable, consists of reporting one or more cases of neurological complications which, on the basis of operative or autopsy findings, represent true neurological disease induced by the anesthesia.[18, 43, 44] The limitations inherent in such reports lie in the fact that the cases reported are almost invariably drawn from an indeterminate sampling population. Such reports prove that neurological sequelae can result from spinal anesthesia but give no indication as to how often this occurs. The report by Kennedy, *et al.*[43, 44] is an example of this. These authors present 12 cases, mainly of arachnoiditis, the majority probably being the direct result of previously administered spinal anesthetics. No reference is made to the number of spinal anesthetics administered during the time required to accumulate these 12 cases. However, the majority of these cases was encountered in a single large metropolitan hospital, though at least one came from elsewhere. If, as is likely, these cases were drawn from a population in which over a half million spinal anesthetics had been administered, then the magnitude of the problem is different than if the cases had been the result of 1,200 spinal anesthetics. The authors of such reports not only fail to state the size of their sampling population, but, by virtue of usually being associated with large teaching hospitals, they also fail to take into account that the complications come from a large geographical area and not just from one city. Such selection of cases often leads to the impression that spinal anesthesia is the only anesthesia associated with major complications. The major complications of general anesthesia are not encountered by such authors because they are so often immediately fatal.

Another approach to the study of incidence is represented by surveys, usually retrospective in design, of hospital experience.[1, 64, 70] This entails tabulation of the number of spinal anesthetics administered over a period of time, together with the number of complications encountered. The complications may be based on the vagaries of memory or on review of hospital records. Such studies involve, at best, one of two assumptions: either that all neurological complications of spinal anesthesia can be (and will be) recognized even in their most subtle forms prior to the time the patient leaves the hospital; or, that the patient will return to the same hospital if neurological symptoms occur after discharge. Neither assumption is valid, even when, as has been suggested, one is dealing with a "captive population" such as a governmental hospital population which the authors consider to be so litigation-minded that the absence of any medical or legal repercussions is assumed to mean that no complications did in fact occur.[71]

The deficiencies inherent in the preceding method have been taken into account and at-

tempts have been made to counteract them by follow-up studies wherein patients who have had spinal anesthesia are contacted after their discharge from the hospital.[7, 26, 72, 76] Questionnaires are usually mailed the patients and the answers serve as the basis for calculation of frequency of neurological deficits. Aside from the fact that such studies usually suffer from being restrospective in design, and aside from bias introduced by the questionnaire itself, such a method suffers from the limitation imposed by interpretation of the medical significance, if any, of the patient's replies. Lay responses are often impossible to evaluate, and these studies must, if they are to accomplish their aims, include provisions for a complete and objective neurological examination of those who claim to have neurological symptoms. Further limitations of time, cost, and patient cooperation make completion of such studies in statistically valid numbers of cases difficult.

While there are several important surveys of the incidence of neurological complications which take into account some of the above factors,[23] there is only one study which has included them all and hence may be regarded as a valid index of the incidence of such complications in at least one hospital. This is the study reported by Dripps and Vandam.[25, 79-81] This study has the advantage of being set up prospectively rather than retrospectively, and not only are statistically valid numbers of cases (10,098 spinal anesthetics administered to 8,460 patients) included, but a control series of 1,000 patients who received general anesthesia is evaluated. The patients were contacted at least six months after anesthesia, thereby allowing time for possible delayed onset of sequelae, and patients who replied that they did have neurological symptoms were examined. There was only one patient in the series who had incapacitating neurological disease following spinal anesthesia, and this was found to be due to an unsuspected spinal cord meningioma. Sixty-six patients complained of subjective feelings of numbness or tingling in thighs, legs, feet, or perineum, but in none were the symptoms progressive or severe and they usually disappeared within one year. In 43 of these 66 patients there were no objective findings, while in 23 there was decreased sensation to pinprick. An additional 3 patients had temporary unilateral footdrop, 2 after spinal and 1 after general anesthesia. Nine patients with unrecognized pre-existing neurological disorders reported transitory exacerbation of symptoms of their underlying diseases.

While the report of Dripps and Vandam indicates that spinal anesthesia can be devoid of major neurological complications, the literature indicates that such is not always the case. It appears, however, that in recent years, the frequency with which such complications occur is less than in the preceding 50 years. This cannot be entirely ascribed to any sudden reticence in reporting such cases, but is in all probability due to a real decrease in frequency. It is also apparent, however, that even in recent years factors may arise which result, usually suddenly, in an inordinately high incidence of neurological complications in one institution. Such factors are undoubtedly operating in certain reports [23] including that of 6 cauda equina syndromes developing within 6 months in a small hospital.[6]

Pathology

The pathological findings associated with neurological complications due to spinal anesthesia are of two major types: those which involve primarily the meninges, and those which involve primarily nerve tissue. In the majority of cases elements of both types of reaction may be observed, but usually one type predominates.

The most frequently encountered lesion involving the meninges is a chronic adhesive arachnoiditis consisting of a proliferative overgrowth of the pia arachnoid to the extent that the subarachnoid space may be obliterated.[17] Such arachnoiditis is usually more pronounced in that portion of the subarachnoid space in which the highest concentration of local anesthetic was present during the anesthesia and so the cauda equina is most frequently involved. In certain cases the lumbar area may be relatively uninvolved while the thoracic area is affected. Arachnoiditis of this type is notoriously chronic in its onset and development.[56] It often shows a distressing tendency to progress inexorably in a cephalic

direction until it involves high thoracic or cervical sections of the cord, areas which were not affected by the original spinal anesthetic. By obstructing normal flow of cerebrospinal fluid, increased intracranial pressure with internal hydrocephalus may result, but the major neurological damage produced by arachnoiditis is the result of interference with the blood supply of the cord itself or of the nerve roots within the subarachnoid space. The nerve roots, the most superficial portions of the cord immediately beneath the pia mater, and the posterior columns of the cord are especially liable to show ischemic changes with chronic adhesive arachnoiditis because these structures normally are less abundantly supplied with blood vessels, but the exact pathological picture and the resulting symptoms vary depending upon the location, extent, and density of the arachnoiditis. In milder forms, only individual nerve roots are involved, with the cord itself remaining unscathed. In severe forms, normal neuronal architecture may be completely lost and replaced by fibrous tissue.

The microscopic findings in chronic adhesive arachnoiditis [17, 43, 84] show the arachnoid to be thickened and replaced by collagenous fibrous tissue. Leucocytic infiltration is rarely prominent, but when present usually consists of lymphocytes. Foreign body giant cells are conspicuous by their absence. One of the more interesting and significant microscopic findings is the presence of a characteristic arteritis affecting especially the vessels of the arachnoid but also found to a lesser extent in other arteries such as those in the pia mater.[10, 24, 35, 38, 59, 91] This arteritis involves primarily the media of smaller arteries and consists of an initial necrosis with swelling and edema formation, followed by thickening as the media is replaced by proliferating fibroblasts. The adventitia may also be involved, but the intima is usually relatively intact. The result of these changes is obstruction of the lumen with consequent impairment of blood flow. The histological changes in nerve tissue in arachnoiditis range from minor alterations in staining properties of nuclei and cytoplasm with some chromatolysis, to degeneration so severe that nerve tissue is no longer recognizable as such. These changes are dependent primarily upon ischemic alterations produced by the attendant arteritis. Though inadequately emphasized in many reports, and, indeed, not even mentioned in some, the characteristic arteritis accompanying this type of chronic adhesive arachnoiditis is of major importance in explaining the pathogenesis and clinical course of many instances of neurological damage due to spinal anesthesia. Whether the arteritis is a consequence of the arachnoiditis, or vice versa, or whether they both represent the same response to a pathological stimulus is unknown at present, but the end result is a histological picture reminiscent of collagen diseases involving arteries and connective tissue in other parts of the body.

A second type of pathological finding involving the meninges and which may be seen due to spinal anesthesia consists of an inflammatory response, usually acute and without arachnoidal proliferation. This meningitis may be either septic or aseptic.[32, 54, 78] It usually has its time of onset within 24 hours of the time the anesthesia was administered. Although aseptic meningitis is usually less severe than the septic type, it may be fatal.[5, 12] Septic meningitis pathologically is identical with the more usually encountered types of infectious meningitis. The subarachnoid space contains purulent exudate and the meninges are swollen, injected, and edematous, with marked polymorphonuclear leucocytic infiltration. Infecting organisms, usually cocci but occasionally gram-negative rods, are found by culture or direct smear. In aseptic meningitis, the meningeal reaction is less pronounced, the leucocytic infiltration is usually lymphocytic, and organisms cannot be isolated. In either type of meningitis, involvement of nerve tissue is usually not striking in the acute stages, but if the acute process develops into a chronic one, nerve damage becomes more conspicuous and the pathological findings resemble those found with chronic arachnoiditis. Although chronic adhesive arachnoiditis may develop without evidence of preceding aseptic meningitis, etiologically they have much in common and aseptic meningitis probably represents a mild form of reaction which in its severe form results in chronic arachnoiditis.

In cases of neurological deficit due to spinal anesthesia which involve primarily nerve tissue,[17, 52] meningeal reactions are minimal or

absent. The histological picture is one of acute myelopathy with destruction of myelin, both in nerve roots and in the cord itself, together with swelling and fragmentation of axis cylinders. The cord changes are most pronounced immediately beneath the pia mater and in the posterior columns. Though wallerian degeneration of axis cylinders produces pathological changes quite distant from the site of maximal nerve damage, the most pronounced changes are usually located in that portion of the subarachnoid space in which the concentration of local anesthetic was highest during the anesthesia. The onset of symptoms is immediate and the neurological deficit is complete and non-progressive. If the acute myelopathy is associated with trauma, variable degrees of subarachnoid and intracordal hemorrhage and leukocytic infiltration are also present, but in the majority of cases there is neurolysis without extravasation of blood or leucocytic reaction. If there is survival for an adequate period of time, connective tissue reaction may also be seen, with gliosis of the cord as well as arachnoidal thickening, but in such cases myelopathy remains the dominant feature.

Etiology

Neurological sequelae of spinal anesthesia may be due to the local anesthetic agent employed, to nonanesthetic drugs or chemicals intentionally injected into the subarachnoid space with the local anesthetic, to contaminating substances unintentionally introduced into the subarachnoid space, and to trauma.

Subarachnoidal reactions to local anesthetics are a function of the histotoxic properties inherent in the local anesthetic employed. The histotoxic potential of some local anesthetics is so low as to be nonexistant for all practical purposes, while other local anesthetics have considerable histotoxic properties. Determination of the histotoxic liability of a local anesthetic is notoriously difficult, depending as it does not only on the criteria of toxicity and the type of tissue studied but also upon species differences. It is almost impossible to determine in advance whether a particular local anesthetic will or will not be associated with an increased incidence of histotoxic reactions when used under clinical conditions to produce spinal anesthesia. Experimental work in laboratory animals will give some information on histotoxicity. Postanesthetic examination of cerebrospinal fluid for chemical changes or pleocytosis will also give some indication of the histotoxic properties of a spinal anesthetic agent. But final proof of the presence or absence of histotoxicity depends upon laborious accumulation and meticulous analysis of large numbers of clinical cases. This can, of course, prove to be dangerous if it develops that the local anesthetic under consideration does in fact possess significant histotoxic properties, for years may elapse before it becomes evident. Stovaine (amylocaine), for example, was employed for spinal anesthesia for many years before it was recognized as possessing inherently greater histotoxic properties than other local anesthetics. It is partly for this reason that when drugs such as Stovaine, cocaine, or apothesine were used for spinal anesthesia, the resulting subarachnoid reaction under both experimental and clinical conditions was markedly different than with other local anesthetics. Such adverse reactions are evidenced not only histologically [23, 75, 82, 90] but also by pleocytosis and abnormal cerebrospinal fluid chemistries.[3, 4, 49, 51, 66, 68] On the other hand, although earlier reports show that local anesthetics such as procaine and tetracaine have occasionally been associated with pleocytosis,[39] more modern studies have indicated that they are devoid of histotoxic properties when properly administered, that there is no significant gross or microscopic reaction,[41, 48] and no significant changes in cerebrospinal fluid have been found [8, 42, 47] following their administration. Procaine and tetracaine have also been employed in hundreds of thousands of cases without untoward neurological effects. The cause of many of the neurological complications of spinal anesthesia reported in the past is related to the histotoxicity of the local anesthetics used. Today histotoxicity is rarely if ever an etiological factor.

Local anesthetics such as procaine or tetracaine, normally without significant histotoxicity, may show such effect when used in excessively high concentrations. Procaine, for example, experimentally produces permanent neurolytic changes in the spinal cord when

injected in concentrations exceeding 5 per cent.[56, 57, 58] Again, neurological complications in the past were at times due to inordinately high concentrations of local anesthetics, but today this is infrequently a factor except when spinal anesthesia is unintentionally produced during epidural anesthesia or nerve blocks.

Attempts have been made to ascribe neurological sequelae of spinal anesthesia to "allergic sensitivity" of subarachnoid structures to the local anesthetic employed. There is no proof that such has ever occurred or even that it could occur. In those few cases in which such allergy has been tested for,[43] the results have been negative. Contact dermatitis of the fingers may result from repeated and prolonged exposure to local anesthetics, but there is no histological or other evidence that truly allergic responses of subarachnoid tissues occur following applications of a local anesthetic such as procaine or tetracaine. Explaining neurological complications on the basis of "allergy" represents essentially a philosophy that blames the patient for iatrogenically induced reactions, a philosophy which may be legally desirable but which is morally and medically indefensible in the light of available information.

A second possible explanation for neurological complications due to spinal anesthesia includes reactions to substances intentionally introduced into the subarachnoid space at the time the local anesthetic is injected. A great number of such substances have been employed in the past with the objective either of altering the specific gravity of the local anesthetic (alcohol, acacia) or of offsetting the depression of sympathetic nerves produced by the anesthesia (strychnine). Much of the earlier work on the histological effects of spinal anesthesia on the cord and meninges is based upon administration of drugs such as Durocaine (procaine, gliadin or acacia, glycerin, and alcohol), Spinocaine (procaine, amyloprocaine, alcohol, and strychnine), and Gravocaine (40 per cent procaine with strychnine).[20] Such studies almost invariably show a significant reaction involving meninges, nerve roots, and the spinal cord. These mixtures are no longer used, at least in this country, so while these studies indicate reasons for the development of neurological complications due to spinal anesthesia in the past, they bear little relation to the problem today. The non-anesthetic drugs now most frequently injected deliberately into the subarachnoid space with a spinal anesthetic are glucose and vasoconstrictors. The former, used to alter specific gravity, is not associated with histological changes in the subarachnoid space.[56] The latter are used to prolong the duration of anesthesia. Despite some initial hesitancy in their use for this purpose, there is no evidence to indicate that the more commonly used vasoconstrictors (epinephrine, phenylephrine) are associated with either histological reactions or increased incidence of neurological complications. The use of catheters for continuous spinal anesthetics results in an increased pleocytosis,[7, 42] but the numbers of cases and their follow-ups are inadequate to prove whether such a technique is accompanied by an increased number of neurological sequelae or not.

Neurological complications may also be due to substances inadvertently and unknowingly injected into the subarachnoid space at the time the local anesthetic is injected. These substances may cause neurolysis or, acting as irritants, they may cause arachnoiditis. Phenol and alcohol, for example, cause prompt, severe, and irreversible acute myelopathy if accidentally injected (usually because of failure to identify ampules correctly). But such gross errors are less frequently the cause of such complications than are unrecognized but repeated contaminations of spinal equipment or drugs by foreign substances. These substances may include talcum powder from surgical gloves, bits of cotton from material used to wrap syringes, and even possibly ions from metallic syringes.[53] But the contamination which has received the most attention recently is that caused by sterilizing solutions and detergents. Sterilizing solutions can contaminate either because the solution used to clean the patient's skin is allowed to drop on spinal needles and syringes, or because invisible cracks develop in ampules of anesthetic solutions sterilized by immersion in germicidal solutions. Entry into anesthetic ampules of contaminants such as formaldehyde and phenol with their consequent injection into the subarachnoid space has been hypothesized as the

cause of subsequent development of both aseptic meningitis [5, 32] as well as acute myelopathy and chronic adhesive arachnoiditis.[6] Storage of ampules in sterilizing solutions is now regarded as malpractice for this reason.[11, 15] Despite widespread recognition of the dangers of contamination by sterilizing solutions, there has been little experimental work attempting to quantitate the effects of different sterilizing solutions and the concentrations required to produce neurological damage. The most extensive work is that by Searles and Nowill.[73] Using rabbits and dogs as experimental animals, they found that 10 per cent phenol and 2 per cent Mercurochrome failed to produce motor paralysis following their subarachnoid injection, nor did dilutions of 3:100 70 per cent ethyl alcohol, 1:1,000 Zephiran, 2:100 chlorophenyl, or 2:100 Bard-Parker Solution. The concentrations required to produce paralysis were 3 or 4:100 70 per cent ethyl alcohol, 3 or 4:100 chlorophenyl, 3:100 Bard-Parker solution, and 3 per cent Mercurochrome. They emphasize that because of species differences these results cannot be applied to humans, but they also point out that contamination of a 2-ml. ampule with 3 or 4 parts per 100 would involve only 0.06 to 0.08 ml. of contaminant, an amount impossible to detect by visual inspection of the ampule. Their data indicate that while surprisingly large amounts of agents such as phenol and Mercurochrome are required to produce neurological damage in experimental animals, other contaminants are highly toxic, thus emphasizing that both concentration and type of contaminating sterilizing solution are of etiological significance. Ferguson [20] also found, on the basis of observations that necessarily were not well controlled, that the amounts of alcohol required to produce neurological deficits in humans was so great that he precluded it as a contaminant responsible for neurological complications. The importance of concentration as well as type of contaminant was further demonstrated by Bergner, *et al.*[6] who, in a single dog, failed to find symptoms or histological reaction 3 months after the intrathecal injection of 1.0 ml. of 1 per cent tetracaine diluted with 1.0 ml. of 10 per cent dextrose and contaminated by 0.5 ml. of a solution containing 1 per cent formaldehyde, 1 per cent gentian violet, and 70 per cent isopropyl alcohol. Despite, however, the difficulty in quantitating the effect of sterilizing solutions in the subarachnoid space, especially in man, such contamination must be strictly avoided under clinical conditions. Failure to do so has resulted in many of the neurological complications reported in the past.

The proposal is also difficult to quantitate that contamination by detergents used to clean spinal anesthetic equipment may result in aseptic meningitis or more serious damage. This possibility was originally presented in 1952 by Winkelman who attributed 11 cases of postspinal neurological complications to such contamination.[87] Examination of the original communication reveals that such contamination was not proven, nor was the ability of such contamination, if present, to produce neurological damage proven. The statement that "a detergent was accidentally injected with the spinal anesthetic" is based on one fact and two assumptions. The fact is that a "mild detergent" was used to wash the syringes and that the syringes were then rinsed only once or twice in tap water prior to being autoclaved. The assumptions are that the detergent remained in the syringes after rinsing in tap water and that it was present in quantities and concentration great enough to produce neurological damage when injected intrathecally. An attempt was made to prove these assumptions by injecting an unstated amount and concentration of this unspecified detergent into the subarachnoid space of one animal (type unstated), following which the animal developed paralysis of the hind legs. No autopsy was performed to demonstrate the pathology present or to rule out traumatic damage to the cord, a likely possibility following spinal anesthesia in cats, dogs, and rabbits,[72] and so this single experiment can hardly be regarded as proof of the hypothesis. This same hypothesis was used in a later report of additional cases by Winkelman,[88] and was also used as the explanation for the case of arachnoiditis reported by Paddison and Alpers in 1954,[65] but again proof was not offered. This problem was examined more objectively by Rendell in 1954.[67] She found an increased cerebrospinal fluid white cell count in each of 9 patients 18–36 hours after receiving dibu-

caine spinal anesthesia administered using syringes which had been stored in the disinfectant, Lysol, whereas in none of the 5 patients given dibucaine spinal anesthetics using syringes which were not stored in Lysol were there any white cells in the cerebrospinal fluid at comparable times. The majority of her patients showing pleocytosis also showed increases in cerebrospinal fluid protein content.

Hurst in 1955 [38] was the first to study experimentally the effects of intrathecal detergents. Using intracisternal injections in rhesus monkeys and determining the effects of the injections by autopsy examinations at various intervals afterward, he evaluated ionic and anionic detergents and antiseptics. The subarachnoid reaction, when present, was the same following all agents. It consisted of relatively mild damage to the superficial nervous structures exposed to the substance injected (abnormal nuclear staining and chromatolysis) and a pronounced cellular proliferation of the arachnoid with marked necrosis of the media and adventitia of meningeal arteries. The incidence of such reactions varied with the drug injected and its concentration. A detergent such as alkyl-trimethyl ammonium bromide required 1.0 ml. of a 0.1 per cent solution to produce a reaction, but detergents such as β-phenoxyethyl-dimethyl-dodecyl ammonium bromide were considerably more toxic. The effective concentration of an anionic detergent such as the sodium salt of a sulfated cetyl/oleyl alcohol mixture was 2.0 per cent, that of a nonionic detergent (an alkylated phenol-ethylene-oxide-condensate) was 0.5 per cent. One antiseptic (6-di-4′-chlorophenyl-diguanidohexane) was extremely toxic in concentrations of 0.02 per cent, while another (a commercial antiseptic containing chloroxylenol and terpineol) required 2.0 per cent. Phenol also required 2.0 per cent to produce a histologically evident effect. Hurst concluded that detergents were of questionable etiological significance in the production of neurological complications, first because the appearance of such complications antedated the introduction of detergents, and, secondly, because the concentration of detergent required to produce a reaction was so high. His former reason may not be valid because, as already mentioned, neurological complications reported prior to the introduction of detergents were in all probability due to other factors. The second point is well taken, and is substantiated by the observation of Bergner, *et al.*[6] that 0.1 ml. of green soap injected into the subarachnoid space of a dog failed to produce neurological deficit.

Joseph and Denson [21, 41] also studied experimentally the role of detergents, using as their test substance TSP (tribasic sodium phosphate, a material commonly found in detergents) and injecting it intrathecally in Macaque monkeys. They contaminated syringes and needles by soaking them in TSP and then, without rinsing, autoclaved them and used them to produce spinal anesthesia. Control animals given spinal anesthesia without contaminated equipment did not show histological changes at autopsy 5 to 9 months later. Five monkeys given spinal anesthesia with equipment contaminated with 1 per cent TSP also did not show histological changes 3 to 8 months later. Of four monkeys given spinal anesthesia with equipment contaminated with 5 per cent TSP, 2 did not show pathological changes 3 and 7 months later, 1 had a slight weakness of one leg ascribed to a dural cyst due to the lumbar puncture, and 1 did not have clinical signs, but at autopsy 3 months after the spinal had moderately severe arachnoiditis. These authors also contaminated syringes in the same manner with "various other detergents" and used the equipment to administer spinal anesthetics to another group of 5 monkeys. Two of these animals received one spinal, one received 2, one 3, and one 4. At autopsy 6–14 months later, all monkeys showed some arachnoiditis, "severe" in 1, "moderate" in 2, and "mild" in 2.

The foregoing indicates that experimentally detergents injected intrathecally can produce reactions involving primarily the pia arachnoid. The extent of the arachnoidal reaction depends upon the detergent employed and its concentration. The data do not prove, however, that contamination by detergents of spinal anesthetic equipment under clinical conditions plays a role in the etiology of postspinal neurological damage in man. Nevertheless, even though such final proof is lacking, the burden of proof must rest with him who

denies that such contamination could result in adverse changes in the subarachnoid space. Such an empiric approach is supported by the fact that those clinics which avoid the possibility of such contamination also report the lowest incidence of neurological complications.

Finally, trauma may be an etiological factor in the production of postspinal complications.[81] Such cases usually are the result of injury to spinal nerves when the spinal needle impinges upon them where they are relatively fixed as they leave the dura at the intervertebral foramina. Nerves in the cauda equina are rarely damaged because of their free-lying position. Such injury to nerves is the result of too lateral a placement of the spinal needle and is recognized by an immediate paresthesia. The postanesthetic symptoms are those of a radiculitis involving the specific nerve root injured. Diffuse involvement of subarachnoid neural tissues is rarely the result of trauma unless subarachnoid hemorrhage is produced, in which case aseptic meningitis is usually caused.[40] Trauma to the cord with consequent widespread neurological damage does not occur unless the lumbar puncture is performed above the second lumbar interspace, the cord usually ending opposite the second lumbar vertebra in adults. The frequent development of meralgia paresthetica after spinal anesthesia remains incompletely explained, but is probably related to the fact that the second and third lumbar roots from which the lateral femoral cutaneous nerve is derived are more frequently traumatized during lumbar puncture than are other roots.

Diagnosis

Neurological complications due to spinal anesthesia must be suspected in any patient developing neurological signs or symptoms within eight months after the anesthesia. As soon as the diagnosis is suspected, immediate steps must be taken to prove or disprove the diagnosis. Under no circumstances should it be assumed that the neurological symptoms are automatically due to the anesthesia, for in a large number of cases it will be found they are due to other causes which may be curable if promptly and correctly treated.

The first step in proving or disproving the diagnosis is a complete neurological physical examination. This must be performed by a physician who is unbiased and objective in his approach to the problem. Physical findings in cases of neurological disorders which are associated with spinal anesthesia but which are not due to the anesthesia vary widely, but the physical findings in cases due to spinal anesthesia usually form characteristic patterns depending upon the pathologic changes present and their extent and duration. If, at one extreme, extensive myelopathy of the spinal cord and nerve roots has occurred, the symptoms will be immediate, severe, and usually nonprogressive, the picture often resembling a spinal anesthesia which "never wore off." Such cases, usually due to intrathecal injection of strongly neurolytic substances, often give a history of severe pain at the time of injection. These patients will exhibit complete sensory anesthesia in the area of peripheral distribution of the involved spinal nerves together with either upper or lower motor neuron paralysis, depending upon the extent of damage, though usually flaccid paralysis predominates. At the other extreme, if myelopathy is less extensive symptoms may be limited entirely to the areas of distribution of nerves in the cauda equina, with function of smaller autonomic fibers being most impaired. In such cases, the symptoms will be referable to dysfunction of rectal and bladder sphincters, alone or in combination, but the symptoms will not characteristically show progression. Any combination of findings between these two extremes may be found depending upon the extent of the injury.

If neurological damage is due to chronic adhesive arachnoiditis produced by spinal anesthesia, the onset of symptoms and the appearance of positive neurological findings may be delayed for weeks or even months, though often, at least in retrospect, subtle neurological defects will be discernible within two weeks. Symptoms of arachnoiditis appear insidiously, but once present they characteristically progress inexorably. The symptoms and physical findings will depend upon the

portion of the subarachnoid space involved, the density of the arachnoidal proliferation, its duration, and whether it "skips" sections of the subarachnoid space or involves it uniformly. The cauda equina is most frequently the area first involved. Because smaller nerve fibers are the first to lose their functional capacity as a result of pressure or ischemia, the autonomic fibers in the cauda equina are the first and most seriously involved as a result of arachnoiditis. For this reason, bladder and rectal sphincters and associated smooth muscles are often involved and the resulting symptoms are often the first manifestation of a developing cauda equina syndrome. These findings may be associated with hypesthesia or anesthesia of sacral and lower lumbar nerves, often first noted when the patient fails to perceive pain when intramuscular injections are made in the gluteal area. It is impossible to predict initially whether arachnoiditis, once established, will progress and, if so, how far it will extend. Usually it will advance cephalad at varying rates. If the arachnoiditis does progress, complete paraplegia may develop together with signs of increased intracranial pressure as cerebrospinal fluid circulation is progressively impaired. If the patient survives, cervical arachnoiditis may develop with subsequent phrenic paralysis and death. The arachnoiditis may, however, be patchy in distribution and not dense enough to occlude the subarachnoid space, and then there will be scattered areas of neurological damage depending upon the specific nerve roots and spinal cord tracts involved.

The physical findings in cases of traumatic injury incurred during administration of spinal anesthesia will be discrete and limited to the specific nerve root(s) involved. Lower motor neuron paralysis will be present if the roots concerned are motor, and painful paresthesias will predominate if the roots are sensory. In either case, spontaneous regression is the rule.

The diagnosis of aseptic meningitis is suspected in the presence of a stiff neck and headache. Systemic reaction is mild, consisting of low-grade fever and little or no leucocytosis.[5] In septic meningitis, the systemic reaction is severe with pyrexia and polymorphonuclear leucocytosis. In either aseptic or septic meningitis, symptoms of cerebritis may develop but usually are not conspicuous. In aseptic meningitis peripheral neurological findings are infrequent and transitory. In septic meningitis the development of permanent neurological disorders depends upon the adequacy of treatment and the tendency of the infecting organism to produce subarachnoid adhesions.

Unless definite contraindications exist, complete neurological physical examination should be followed by diagnostic lumbar puncture even though the information so obtained may be only of negative value. In cases of acute myelopathy, cerebrospinal fluid usually shows a slight elevation in protein and a slight lymphocytic pleocytosis in the first week or ten days, but thereafter the spinal fluid is remarkably normal. In chronic adhesive arachnoiditis, spinal fluid will frequently show little if any change in protein content and no significant pleocytosis, but spinal fluid may often be difficult or impossible to obtain by lumbar puncture because of obliteration of the subarachnoid space. When present, it is frequently obtainable in only small amounts and in such cases the Queckenstedt test will be positive. The cerebrospinal fluid will be negative in cases of traumatic neuritis due to spinal anesthesia, but in cases of aseptic meningitis there will be pronounced elevation of spinal fluid protein and a marked increase in the number of lymphocytes. These subside within a few days and should always be regarded as pathological for, as already mentioned, modern spinal anesthesia with commonly used drugs is not associated with significant changes in cerebrospinal fluid. In cases of septic meningitis, spinal fluid changes depend upon the infecting organism but there is usually increased protein with polymorphonuclear pleocytosis. In all cases of suspected meningitis, attempts to isolate organisms should be made by direct smear and by culture.

Following diagnostic lumbar puncture, myelography should be considered. It should not be employed unless there is evidence of subarachnoid block, and so should be avoided in straightforward cases of acute myelopathy or meningitis. In arachnoiditis myelography will aid in determining the extent and level of a subarachnoid block and will also differ-

entiate other causes of block such as tumor. Myelography should nevertheless be undertaken only cautiously in suspected cases of arachnoiditis, for the precedure itself is associated with a mild but definite subarachnoid inflammatory response which might accentuate a pre-existing chronic arachnoiditis. Injection of air instead of liquid opaque substances into the subarachnoid space may provide at least part of the information desired in such cases and will not be associated with as much reaction. It may then be followed by routine myelography when indicated.

The most important single test for the diagnosis of neurological complications due to spinal anesthesia is electromyography.[60, 61] The value of this test lies first in its ability to differentiate with considerable accuracy those neurological disorders of extradural origin from those of intradural origin. Because spinal anesthesia cannot cause extradural neuropathies, this becomes a most important point in identifying many of the lesions which make their appearance coincidental with spinal anesthesia but which are not causally related to it. For example, in cases with extensive motor paralysis, normal electromyographic activity of the paraspinal muscles eliminates spinal anesthesia as the cause of the paralysis. Secondly, if electromyography is performed at the correct time it will differentiate between lesions which antedated spinal anesthesia from those which bear a direct temporal relation to the anesthesia. If, for example, there is electromyographic evidence of wallerian degeneration in a paralyzed muscle such as the gastrocnemius one week after spinal anesthesia, then the cause of the paralysis cannot be related to the anesthesia but must be looked for elsewhere because such electromyographic changes require more than a week to develop. And, finally, electromyography is of value in determining the precise level of spinal cord damage and differentiating those cases due to the anesthesia from those due to other causes. The value of electromyography has been so conclusively demonstrated by Marinacci [61] that not only must it be employed in every suspected case but no proof of cause and effect can be established unless it is employed and employed correctly.

Treatment

Treatment of acute myelopathy and chronic arachnoiditis due to spinal anesthesia is primarily supportive and directed towards rehabilitation and prevention of the urological, nutritional, and pulmonary complications associated with paraplegia. There is no specific therapy. Cortisone has been advocated both systemically and intrathecally in cases of arachnoiditis in hopes of decreasing fibrous proliferation; while reports of its value remain conflicting,[29, 28] its use, at least systemically, would appear justifiable on theoretical grounds. Surgical intervention may be required to relieve subarachnoid obstruction with increased intracranial pressure due to adhesive arachnoiditis, but unfortunately such measures are usually only palliative.

Treatment of aseptic meningitis is expectant, the condition being benign and self-limiting in the vast majority of cases. In septic meningitis, treatment consists of the administration of appropriate antibiotics after isolation and identification of the infecting organism and after determination of its sensitivity to antibiotics.

Treatment of postspinal neuritis due to trauma associated with spinal anesthesia is also expectant, the condition again usually being self-limited.

Prevention

Because treatment of neurological complications due to spinal anesthesia is so unsuccessful once they have developed, prevention becomes the main and best approach to the problem. The successes reported in decreasing the incidence of neurological sequelae to the vanishing point testifies to the efficacy of prevention in managing the problem.

The first consideration in prevention concerns the histotoxic properties of the local anesthetic agents employed. Procaine and tetracaine, as has been pointed out, are conspicuously devoid of histotoxicity in the subarachnoid space, and have been and are widely regarded as safe anesthetics. Clinical experience over many years in hundreds of thousands of cases confirms their value and safety in spinal anesthesia. The same is not necessarily true for the many other local

anesthetics available for spinal anesthesia. None of them has had their histotoxic properties in the subarachnoid space clinically and experimentally as fully documented. Neither has any been used in statistically large enough series of cases (with adequate follow-ups), to indicate whether under clinical conditions they are as devoid of neurologic complications as are procaine and tetracaine. Certain of them may eventually prove to be as safe as procaine or tetracaine, but before using them the anesthetist should bear in mind that an increased toxicity may only become apparent after many thousands of cases and after many years of use. The literature of the last 60 years lists over 30 local anesthetics which have been used for spinal anesthesia before being abandoned after it gradually became apparent that they had inherent neurotoxic qualities. Because two proven agents are available, and because no other local anesthetic has any demonstrable advantages over these two in spinal anesthesia, prevention of neurological sequelae must include avoidance of indiscriminate use of new and different local anesthetics merely because they are new and different and produce anesthesia.

Histotoxicity being a function of concentration, prevention of neurological complications also includes strict limitation of the concentration of local anesthetic employed. Procaine should not be used in concentrations greater than 5 per cent, tetracaine in concentrations greater than 0.5 per cent. Dosage being one determinant of the concentration to which subarachnoid structures are exposed during spinal anesthesia, it probably also should be limited, although dosage is usually limited to avoid excessive spread of the anesthetic. Single intrathecal injections should not exceed 200 mg. for procaine or 18 mg. for tetracaine.

Prevention of neurological sequelae includes strict asepsis. This involves shaving the patient's back, preoperative washing of the back with soap and water the night before, and use of appropriate bactericidal solutions on the patient's back immediately prior to lumbar puncture. It also includes use of sterile drapes at the time of lumbar puncture as well as a mandatory surgical scrub by the anesthesiologist prior to putting on sterile surgical gloves for the lumbar puncture. Spinal sets and ampules must be sterilized by autoclaving; 255–260 F under 18–20 pounds pressure for 30 minutes has proven adequate. Sterilizing of ampules must not be achieved by soaking in germicidal solutions. The use of ethylene oxide for sterilizing spinal equipment should be avoided until experimentally proven to be safe. Use of an introducer may be wise to prevent not only bacterial contamination of the spinal needle as it passes through skin which cannot be rendered completely sterile, but also to prevent chemical contamination of the needle by sterilizing solutions remaining on the skin.

Chemical contamination must be avoided by use of glass syringes, by preventing the solution used to clean the skin from dropping on the anesthetic equipment, by autoclaving drugs,[11] and by meticulous cleaning of spinal syringes and needles prior to their being autoclaved. Such cleaning should rely upon scrubbing with soap and water, followed by copious rinsings with ether and distilled water. Detergents, germicides, and chemicals used to dissolve blood clots should not be used in cleaning spinal sets. Spinal sets should be wrapped in lint-free coverings. Finally, starch or talcum used on gloves must be prevented from contaminating spinal sets by putting on such gloves some distance away from the set and, preferably, by rinsing the outside of the gloves with saline.

Trauma must be avoided by proper positioning of the patient, a thorough knowledge of the anatomy involved, and gentle but firm motions rather than abrupt plunges when inserting the spinal needle.

Prevention of neurological complications by avoidance of spinal anesthesia in patients with pre-existing diseases of the central nervous system has been advocated [36, 80] but despite widespread acceptance of the principle involved, proof of the validity of the principle is lacking. If pre-existing spinal cord disease predisposed to neurological complications of spinal anesthesia, one would expect to find an increased incidence in the older age groups because of spinal cord changes associated with the aging process.[63] There is, however, no relationship between age and incidence of postspinal sequelae. Certainly there is no reason to avoid spinal anesthesia in diseases involving

only the cranial portions of the central nervous system, providing they are not associated with increased intracranial pressures. Elderly patients with cerebral arteriosclerosis or parkinsonism, for example, often do better with low spinal anesthesia for perineal or lower extremity surgical procedure than they do with general anesthesia if the blood pressure is maintained. But in patients with diseases involving the spinal portion of the central nervous system, administration of spinal anesthesia should be avoided despite the lack of proof that spinal anesthesia will make the condition worse. This should be done if for no other reason than so many of these disorders are progressive or subject to spontaneous exacerbations. The tendency has been and undoubtedly always will be to blame spinal anesthesia for such progression or accentuation even though the same neurological changes might have occurred in the absence of spinal anesthesia. Spinal anesthesia should not be administered in symptomatic conditions involving the cord or in conditions where spinal cord involvement is known to occur but where symptoms of such involvement are not yet present. The latter category includes patients with pernicious anemia, patients with asymptomatic positive spinal fluid serology, and patients with tertiary syphilis and undetermined spinal fluid serology. Common sense and medico-legal considerations may proscribe spinal anesthesia in situations where the cord is uninvolved but where spinal nerve roots are involved. Such situations include patients with metastatic carcinoma to the spinal column or a herniated nucleus pulposus. In paraplegics where the spinal cord is so damaged as to be functionless, spinal anesthesia may be employed on the basis that no further damage can result.[69]

Cranial Nerves

Although dysfunction involving almost all of the cranial nerves has been reported following spinal anesthesia,[77] the abducens is the most frequently involved.[12, 34, 37, 45, 77] The reported incidence varies from 1 in 300 to 1 in 8,000, but the literature indicates that this is a less frequent complication today than in the past. Usually unilateral, abducens palsy manifests itself most frequently between the second and fifth postoperative days as a diplopia or, less often, a blurring of vision. It is almost always associated with postspinal postural headaches. The etiology has been ascribed to a direct toxic effect of the local anesthetic on the abducens nucleus lying in such close proximity to the fourth ventricle [1] as well as to an inflammatory process involving the nerve itself.[24] The most likely explanation, however, is that there is mechanical trauma to the abducens nerve caused by stretching as a result of changes in intracranial pressure. The frequent association of postspinal headaches with abducens palsy supports this theory. The length of the abducens nerve has been mentioned as making it susceptible to such stretching, but length alone is not a factor for the trochlear nerve is longer but rarely involved. The susceptibility of the abducens nerve to stretching is related to the fact that it is relatively fixed at its entry into the cavernous sinus and at its attachment in the pons, and that in its course it is exposed to two points of pressure: where it crosses the apex of the petrous portion of the temporal bone, and where the anterior inferior cerebellar artery crosses it anteriorly at right angles between the pons and the occipital bone. Changes in cerebrospinal fluid dynamics following puncture of the lumbar dura and chronic loss of spinal fluid would be expected to produce stretching of the abducens nerve at either of these two sites, though it would appear to be more likely to occur at the apex of the petrous bone. Diagnosis is established by demonstrating paralysis or paresis of the lateral rectus muscle. Abducens palsy is to be differentiated from latent esophoria which may become manifest postoperatively.[27] Treatment of abducens paralysis is conservative, with symptoms disappearing as cerebrospinal fluid dynamics are restored. Preventive measures are those employed for prevention of postspinal headaches, especially the use of small spinal needles and adequate hydration.

Medico-Legal Considerations

Anglo-Saxon legal tradition is based on the concept that a person is assumed to be innocent until proven guilty. Medico-legally this

tradition is carried out in the principle that a plaintiff instituting suit for malpractice against a physician must prove negligence. Unless such negligence can be legally proven, malpractice cannot be established. There are situations, however, in which events have taken place which are in themselves so obviously the result of negligence that expert medical testimony is not required to prove negligence, a lay jury being capable of establishing this on the basis of facts alone. An example of this is the sponge or instrument remaining in the peritoneal cavity following laparotomy. The legal term used in such situations is *res ipsa loquitur*, literally "the thing speaks for itself." [82] The doctrine of *res ipsa loquitur* has been applied to neurological complications following spinal anesthesia.[12] The fact that a patient has had a spinal anesthesia and has developed a neurological deficit does not, however, in itself prove that the deficit is due to the anesthesia, nor does it prove negligence in administration of the anesthetic. The application of the doctrine of *res ipsa loquitur* removes, however, the necessity for such proof and says, in effect, that any physician administering a spinal anesthetic places himself in a special Alice in Wonderland legal world where proof is no longer of any consequence. The doctrine of *res ipsa loquitur* in such cases becomes a travesty of justice. The anesthetist, according to this doctrine, is responsible for neuropathies due to the surgical procedure, for thrombosis of the anterior spinal artery, for spinal cord meningiomas, for the onset of multiple sclerosis, and for anything and everything that neurologically befalls the patient. The illogic of *res ipsa loquitur* is demonstrated by the fact that neurological damage identical to that seen after spinal anesthesia may also be seen after general anesthesia,[1, 9, 14, 19, 22, 74, 76, 89] and by the fact that when properly evaluated very few postspinal neurological complaints are found to be due to the anesthesia.[60] The tendency of insurance companies to follow such *post hoc ergo propter hoc* reasoning compounds the problem and further restricts the physician in practicing medicine on the basis of purely medically acceptable facts.

To prove that neurological damage is due to spinal anesthesia it must first be proven that the causative lesion is intradural in location. Secondly, it must be proven that temporally it is at least possible that the onset of symptoms coincided with administration of the anesthesia and that such symtoms did not antedate the anesthesia. Thirdly, it must be proven that the intradural pathologic change is histologically a type which can be associated with spinal anesthesia. And, finally, it must be proven that this change is actually due to the anesthesia. Even in cases of chronic adhesive arachnoiditis following spinal anesthesia, such proof is difficult to obtain because chronic adhesive arachnoiditis can develop without any relationship to spinal anesthesia.[60] Even if all the above can be proven, there still remains the necessity for proving negligence on the part of the anesthetist before malpractice can be established. Unless some break in technique can be proven which results in the introduction of one of the etiological factors discussed above, proof of negligence cannot exist even though a lesion such as arachnoiditis may have developed. Abandoning the doctrine of *res ipsa loquitur* will allow such proof to be obtained in a limited number of cases and thereby will contribute to the quality of medical care by removing the stigma attached to an otherwise valuable form of anesthesia.

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NARCOTIC ANALGESIC Twenty courses of injection of morphine or dextromoramide were given to ten different patients with chronic continuous pain. 10.3 mg. of dextromoramide were estimated to be equivalent to 10 mg. of morphine sulfate so far as duration of relief was concerned. When considering the number of doses providing more than 1.5 hours of relief to the patient, 4.9 mg. of dextromoramide were estimated to be equivalent to 10 mg. of morphine sulfate. Euphoria was more frequently reported with 5 and 10 mg. of dextromoramide than with morphine or placebo regimens. No differences in other side effects, blood pressure, pulse, or respiratory rates were observed for comparable drug regimens. (*Bauer, R. O., Free, S. M., Jr., and Bowen, E. H.: Measurement of Chronic Pain Relief Utilizing Dose Response of Dextromoramide Against Morphine and Placebo, J. Pharmacol. Exp. Ther. 131: 373 (Jan.) 1961.*)

SUCCINYLCHOLINE In 39 of 41 adult patients given repeated injection of succinylcholine a slowing of heart rate occurred. In more than two-thirds of the cases this slowing was due to sinus bradycardia. Various abnormalities of conduction and excitation occurred including ventricular standstill for seven seconds in one instance. The larger repeat doses produced the more striking effects. Atropine given intravenously prior to the succinylcholine in 1 mg. dosage prevented these changes. The changes were related to large intermittent injections, not to the total dosage. (*Lupprian, K. G., and Churchill-Davidson, H. C.: Effect of Suxamethonium on Cardiac Rhythm, Brit. Med. J. 2: 1775 (Dec. 17) 1960.*)